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Radiogenic Breast Cancer: Age Effects and Implications for Models of Human Carcinogenesis

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Introduction. Studies of populations exposed to ionizing radiation have led to the identification of a preventable cause of cancer in our society. Over the years preventive measures have been taken to reduce population exposure, including more conservative use of medical radiation, reduction of patient exposure from medical x-ray equipment and stringent environmental and occupational radiation protection guidelines. These measures undoubtably reduce the cancer burden in society. For example, children are no longer irradiated for enlarged thymus glands, tuberculosis patients no longer receive fluoroscopic screening, thorotrast is no longer used as a radiographic contrast medium, mammography exposures have been reduced by an order of magnitude during the last decade, and uranium miners, radiologists and luminescent watch makers are no longer exposed to high levels of radiation. Radiation studies, however, have also provided insights into mechanisms of cancer, and observations made from human studies are now being incorporated into theories of carcinogenesis.

Radiation Studies. The increased risk of human breast cancer following irradiation has been more thoroughly studied than any other radiogenic tumor, with the possible exception of leukemia.[5,8,17] Large-scale studies have found dose-dependent increases in breast cancer incidence in women with pulmonary tuberculosis whose artificial pneumothorax treatment was monitored by fluoroscopic chest examination,[3,18,23] in Japanese women exposed to the atomic bomb,[20,32,34] and in women treated therapeutically with x ray for acute[21,27] and chronic[1] breast conditions. These studies indicate:[5,8,17]

(1) that the underlying relationship between radiation dose and breast cancer incidence is most consistent with linearity, even at doses under 50 rad,
(2) that fractionation does not appear to diminish risk,
(3) that radiogenic cancers do not begin to be apparent until perhaps 10 years or more post-irradiation,
(4) that risk continues throughout life or at least for 40 years,

(5) that the patterns of age-specific incidence of breast cancer are the same for exposed and nonexposed women, differing only in magnitude,
(6) and that age at exposure is the most important factor influencing subsequent risk.

Of these major findings, the association with age, and risk factors associated with age, have formed a basis for the development of several models of hormonal carcinogenesis.[16,22] These observations are discussed in detail below.

Age at exposure. Apart from the radiation dose, the major determinant of subsequent breast cancer risk is the age at exposure. The three major studies to date provide strong evidence for cancer induction in females exposed at ages 10-39, with girls 10-19 years of age having the greatest risk (Table 1).[5,8,17]

Table 1
Age-specific risk estimates,[8] excess cancer(±1s.d.)/10^6WY-rad

Age at exposure	Atomic Bomb Survivors[17]	Massachusetts TB-Fluoroscopy[3]	Rochester Mastitis[27]
0-9	0.0	...	...
10-19	9.2±2.2	8.7±3.1	a
20-29	2.9±0.88	3.8±3.1	6.3±2.0
30-39	4.9±2.5	(6.9±4.5)[a,b]	9.4±3.4
40-49	-1.0±0.45	a,b	(52.1±21.0)[a]
50+	3.3±2.2	...	...
All ages	3.6	6.2	8.3

[a]Estimate based on small numbers and may be misleading.
[b]Observed cancers not in excess of population expectation.

Given the variation in the nature of the exposures, as well as the substantial differences in the populations exposed, the similarity of age-specific risk estimates is remarkable, particularly in the younger ages where the numbers are large enough to provide stable estimates. It is interesting that American women who are at high natural risk of breast cancer,[19] are at comparable risk of radiogenic cancer with Japanese women who are at low natural risk. Crude estimates of radiation risk suggest that Japanese women are at lower risk of radiogenic cancer, but this is because the Japanese population had higher proportions of very young and very old women who thus far seem to be at much lower risk. The best estimate of risk among American women exposed after age 20 is 6.6 excess cancers per million women per year per rad (6.6/10^6WY-rad) after a latent period of about 10 years.[5,8]

To date, there is little evidence that radiation exposures before the age of 10 carry any future risk of radiogenic breast cancer. Among atomic bomb survivors, no excess breast cancers (only 5 total) have occurred among 9,300 women who were under age 10 at exposure and followed to age 30-39.[17,32] These women may not yet be old enough for a risk to have been detected. This seems unlikely, however, since: (1) among 4,200 women exposed at ages 5-9 and followed to age 30-39, only 3 breast cancers occurred, whereas for 5,100 women exposed at ages 10-14 and followed to the same age (30-39 yr), 13 breast cancers had occurred;[17] (2) a recent followup, adding 4 more years of mortality observation, i.e., to age 34-43, has failed to demonstrate an excess risk in those aged 0-9 at exposure;[14] and (3) in a study of 1,200 women exposed as infants to high dose irradiation for enlarged thymus glands, no breast cancers have been reported despite follow-up periods up to 40 years,[11] although the radiation fields may not have completely included the breasts in all cases. Further observations of the A-bomb survivors should provide a definitive answer to whether the immature breast is in fact relatively resistant to radiation damage. If it is, it may be that radiation damage is repaired before the proliferation of breast tissue during menarche, that there are few breast cells at risk for transformation, or that for other reasons breast tissue may not be susceptible to carcinogens before breast budding.

Adolescence, including menarche, appears to be the period of greatest risk for the induction of subsequent breast cancers.[3,23,32] Exposures at ages 10-19 carried the greatest risk for atomic bomb survivors ($9.0/10^6$WY-rad) and TB-fluoroscopy patients ($8.7/10^6$WY-rad).[5] Studies of atomic bomb survivors indicate that women exposed at ages 10-14, around the time of menarche (ave=14.5yr), had the greatest increased incidence of breast cancer.[20,32] The Massachusetts survey of TB-fluoroscopy patients also reported the highest risk for women exposed just before or during their first menses, although the numbers of breast cancers were quite small (3 observed vs 0.28 expected).[4] Possibly, exposures that occur just before menarche, during the period of breast budding and hormonal changes, are especially damaging.[4]

All studies, with the exception of the mastitis series,[27] indicate that radiogenic risk falls with increasing age at exposure from menarche to menopause. This is particularly apparent for the TB-fluoroscopy series[3] where no excess breast cancers were found in women exposed after age 30, and in a Swedish study[1] of women irradiated for benign breast conditions.

Data on women exposed after age 50 are sparse, e.g., only 3 breast cancers occurred in such women in the A-bomb survivors[17] exposed to greater than 100 rad, but the risk associated with such exposure appears to be quite low.

Menopause. Exposures occurring around the time of menopause also appear to carry little or no risk. The atomic bomb survivor study showed no excess risk in more than 2,000 women exposed during their forties.[32] In fact, a significant negative dose-response was reported, i.e., increased dose resulted in decreased breast cancer incidence. This anomalous negative dose-response for Japanese women may be associated with these women receiving total-body exposure, including ovarian irradiation. A study in Hiroshima indicated that amenorrhea occurred in over half of the women aged 40-49 at the time of the bombing.[25] Amenorrhea was permanent for most of these women, whereas it was transient for all women exposed under age 35. Possibly, the disruption of ovarian function for those aged 40-49 at exposure may have decreased subsequent breast cancer risk.

Women undergoing radiation castration have shown significant decreases in death due to breast cancer.[30] Similarly, studies of cervical cancer patients who received large therapeutic doses to the pelvis and ovaries have also shown a decreased risk of developing breast cancer as a second tumor.[15] Particularly provocative findings from these studies are: (1) the decrease in risk of breast cancer appears to be greater than that experienced by women having undergone surgical castration at similar ages; and (2) the protective effect of ovarian irradiation applies also to exposures incurred after the ages of natural menopause, when surgical intervention has no effect.[33] One possible explanation for these findings is that irradiation might produce selective killing of cells in the ovary. Perhaps the estrogen-producing cells are more sensitive to cell killing by irradiation than androgen-producing cells. Irradiation coupled with pituitary hormonal stimulation to the ovary might produce a relatively higher androgen/estrogen ratio in peri- and post-menopausal women that could possibly retard the manifestation of an already induced breast cancer (S. Korenman, personnal communication). At least one other study has reported a low breast cancer risk among women with relatively high levels of endogenous androgens as measured a relatively short time prior to diagnosis.[6] In any event, the effect of ovarian irradiation on subsequent breast cancer risk appears to be an important area for further evaluation.

Pregnancy, Parity, and Lactation. Full-term pregnancies have a profound effect on subsequent breast cancer risk with risk rising with increasing age at first birth, and nulliparous women being at greatest risk unless first pregnancy occurs after about age 35.[19] The TB-fluoroscopy study[4] indicated that nulliparous women (8.7 cancers/10^6WY-rad) were at increased excess risk of radiogenic cancer when contrasted with women exposed before (0.9/10^6WY-rad) or after (0.4/10^6WY-rad) their first pregnancy, but at less risk than women exposed at the time of pregnancy (17.1/10^6WY-rad). The numbers, however, were small and require confirmation. It is noteworthy that a full-term pregnancy after irradiation appeared to lower the risk of radiogenic breast cancer, i.e., exposed nulliparous women who years later became pregnant were at lower risk than exposed nulliparous women who remained nulliparous.[4] Interestingly, a study of dogs that received whole-body irradiation also found an increased risk of death due to mammary tumors in nulliparous but not parous beagles.[7]

The women irradiated for postpartum mastitis[27] had all just given birth, and experienced the largest age-specific risks.[5,17] In contrast to all other experiences, the radiation risk appeared to rise slightly with increasing age at exposure, and was high among those aged 30-44 at exposure. A recent animal experiment[13] has found high excess cancers in rats when exposure occurred during pregnancy or lactation; and it is conceivable that the inflamed and lactating breasts at the time of exposure may have influenced risk in the mastitis patients. In the mastitis series it was also noted that exposure just after a late first pregnancy, i.e. after age 29, carried a greater risk than exposures after earlier first pregnancies, and it was recommended that intense screening of so called high risk women by mammography for early detection of breast cancer be done cautiously for women who were nulliparous or over age 30 at the time of their first delivery.[28]

It has been suggested that reproductive history influences the latent interval between exposure and clinical diagnosis of breast cancer,[35] supposedly through an acceleration of tumor growth by a pregnancy in a small number of women. If this were a widespread phenomenon, however, it might be expected that the average latent period would be longer for nulliparous women than for women irradiated prior to pregnancy, but this was not the case in the Massachusetts TB-fluoroscopy study. The average latent period was 23.4 yr for nulliparous women and 28.8 yr for parous women; the average ages at exposure were 26.4 yr and 21.1 yr, and the average ages at diagnosis for breast cancer were 49.8 yr and 49.9 yr,

respectively (J.Boice, unpublished data). The hypothesis, however, deserves to be tested in a larger series.

Sex. Radiation-induced breast cancer appears predominantly in women. Males, of course, do have breasts, although minimal ductal tissue. The fact that male breasts do not experience periodic endocrine stimulation may be related to the small incidence of natural and radiogenic breast cancer. To date, no male breast cancers have been reported in followup studies of atomic bomb survivors,[2] TB-fluoroscopy patients,[23] or thymic irradiated children.[11]

Summary of Human Studies. The following generalizations, based on relatively substantial data, are consistent with the human studies on radiation-induced breast cancer:

(1) adolescent exposures carry the greatest risk, especially exposures around menarche;
(2) risk appears to fall with increasing age at exposure from menarche up to the time of menopause;
(3) latency is inversely related to age at exposure;
(4) the age-specific incidence patterns of breast cancer are the same for exposed and nonexposed women, differing only in magnitude; and
(5) and risk continues thoughout life or at least for 40 years.

The following tentative generalizations are based on less substantial data:

(1) the immature breast, and perhaps also the post-menopausal breast, may be relatively radioresistant;
(2) exposures during and immediately after pregnancy may be particularly hazardous;
(3) nulliparous women appear to be at greater radiation risk than parous women;
(4) exposed women who remain nulliparous may be at greater risk of radiogenic breast cancer than nulliparous women who later become parous;
(5) and ovarian irradiation may reduce risk beyond the effect of castration.

Many of these conclusions are receiving further evaluation in ongoing followup and case-control studies.

Hypotheses on Breast Carcinogenesis.

The observations made in human studies of radiation-induced breast cancer can be or have been incorporated into general models of breast carcinogenesis.

1. Previous Hypothesis. Prior to many of the observations reported in this paper, MacMahon, Cole and Brown[19] described in clear detail how the epidemiology of human breast cancer indicates that a woman's lifetime risk of breast cancer appears to be determined to a substantial extent during the early years of reproductive life. Their interpretation of this pattern was that some aspect of estrogen metabolism in the years after menarche may be linked to breast cancer risk throughout life. A number of observations from the studies of radiogenic breast cancer outlined above support the importance of early reproductive life in the etiology of breast cancer. For example: (1) radiation exposure around the time of menarche appears to incur the greatest risk; (2) irradiation before menarche seems to carry little or no risk; (3) risk of exposure after menarche appears to fall with increasing age at exposure; (4) the age-specific incidence patterns of breast cancer are similar for exposed and nonexposed women, differing only in magnitude; i.e., although exposures may have occurred as early as adolescence, the clinical presentation of breast cancer did not occur until the ages normally associated with increased incidence, implying that non-radiogenic cancers may also have been initiated during a similar period in early reproductive life.

2. Recent Hypotheses.

(a) Two-stage model. Moolgavkar, Day and Stevens[22] have recently elaborated upon a two-stage model for breast carcinogenesis. The model assumes that two discrete and irreversible events are required for cell transformation. Since each event must occur during cell division, tissue growth and rapid cell turnover would influence susceptibility. Observations made in atomic bomb[32] and TB-fluoroscopy studies[4,5] were incorporated into this model, under the assumption that radiation affects breast tissue by transforming a proportion of susceptible normal cells into intermediate cells. It is the interpretation of these authors that: (1) The absence of a radiation effect in women exposed under age 10 is because few cells are dividing before the period of breast development, i.e., there are few susceptible cells at risk; (2) the reported decreased radiation risk in parous women compared to nulliparous women[4] is consistent with the first full-term pregnancy reducing the number of susceptible cells in parous women, perhaps from the enhancement of breast cell differentiation by a pregnancy; and (3) the fact that radiation-associated risk is highest at puberty and falls with increasing age at irradiation is consistent with a proliferative advantage of intermediate cells, in which one of the two irreversible events has already occurred, a proliferative advantage that would be greatly reduced at menopause when a decrease in the turnover rate of breast epithelium is accompanied by involu-

tion and dysfunction. In other words, the longer the period between irradiation of susceptible cells and menopause the longer the time for radiation-induced intermediate cells to proliferate and the greater the risk.

(b) Estrogen window. Korenman[16] has recently modified two earlier hypotheses concerned with the protective effect of progesterone[9,26] into an estrogen window hypothesis that assumes that endocrine status influences susceptibility to environmental carcinogens. The actions of estrogen and prolactin, unopposed by the action of progesterone, are assumed to increase susceptibility of the mammary epithelium to environmental carcinogens. Two main induction periods, or "windows" are proposed. These are the periods in a woman's life characterized by increased estrogen and diminished progesterone secretion. The first window opens with the onset of ovarian activity before menarche and closes at the onset of regular ovulatory menstrual cycles. The second window opens in the peri-menopausal period with the appearance of irregular, prolonged follicular phase, and anovulatory cycles, and closes with the cessation of ovarian function. The hypothesis assumes that breast tissue is particularly susceptible to environmental carcinogens when these endocrine windows are open, and is relatively refractory to carcinogenesis at all other times. Several observations from radiation studies were noted by the author as being consistent with this model. (1) The lack of a breast cancer excess in atomic bomb survivors exposed under age 10 is consistent with this being prior to the opening of the first endocrine window. (2) The increased susceptibility of the breast to exposures just before and around menarche[3,32] was considered compatible with this being the time when the first window is open. (3) The absence of a significant excess risk among atomic bomb survivors and TB-fluoroscopy patients exposed at ages 30-49 is consistent with this being after the first window was closed and prior to the opening of the second. (4) The nonstatistically significant risk reported for atomic bomb survivors exposed after age 50 was considered possibly consistent with the opening of the second window. (5) The concordance of the patterns of age-specific incidence curves between exposed and nonexposed Japanese women, differing only in magnitude, was considered consistent with the hypothesis that a long latent period applies to both radiogenic and non-radiogenic cancers.

As can be seen, the credibility of models for the hormonal carcinogenesis of human breast cancer can be tested and new models developed by relying on observations from epidemiologic studies of radiogenic breast cancer. The fact that several models are consistent with the same set of observations is not surprising, given the similarity these models have to

each other. We anticipate, however, that these models could be meaningfully tested and appropriately altered by incorporating a number of other observations concerning radiation-induced breast cancer. With respect to current observations, it would be most interesting to learn how the following observations would fit into or alter existing models: (1) the very high risks possibly associated with exposures occurring during pregnancy in TB-fluoroscopy patients,[4] and those definitely associated with exposures just after pregnancy in postpartum mastitis patients;[27] (2) the apparent increase, or at least absence of a decrease, in risk with age at exposure in patients irradiated for postpartum mastitis;[27] (3) the possible increased risk associated with exposures after a late first pregnancy contrasted with exposures after earlier pregnancies;[28] (4) the protection afforded by a pregnancy following exposure in nulliparous women;[4] and (5) the absence of a radiation effect of exposures during the peri-menopausal period in atomic bomb survivors.[32]

Although radiation-induced breast cancer is relatively well studied, a number of associations are not as yet adequately investigated and might very well contribute to the refinement of existing models. Included are evaluations of the relationship between radiation and other breast cancer risk factors. For example, is the effect of radiation influenced if the exposed woman has a relative who developed breast cancer, has a personal history of breast cancer, is obese or has had prior benign breast disease? It would also be useful to evaluate further the effect of ovarian irradiation, the effect of breast irradiation during and just after pregnancy, and the effect of radiation on the immature and the post-menopausal breast.

Models of carcinogenesis for other tumors. Radiation studies are perhaps more readily interpretable than studies of some other environmental carcinogens because exposure generally occurred during a short period of time, can be identified and quantified, and latent period, age susceptibility and period of life-time risk can be evaluated readily. If intensive evaluation of these observations have already been profitably incorporated into models of breast carcinogenesis, perhaps equally important will be similarly intensive studies of radiation-induced cancer of other sites. Such studies could lead to the alteration of a variety of existing models, or assist in the development of new models of human carcinogenesis. Studies of tumors that react to radiation in a similar fashion as the breast, e.g., the thyroid, or in an opposite fashion, e.g., bone marrow-leukemia, might be particularly instructive.

Both breast and thyroid cancers are under hormonal control, occur at higher rates in females in both exposed and non-exposed populations, and occur in subcutaneous organs. For both, radiogenic risk appears to fall with increasing age at exposure, and both are associated with linear or near-linear dose-response relationships.[5,10,11,17,29] The risk of radiogenic thyroid cancer appears greatest if exposure occurs during childhood and this has been interpreted as indicating that rapidly proliferating cells injured by radiation could be more likely to develop abnormally than cells irradiated in later life.[10] As noted, this analogy holds for the breast as well.[4] Finally the excess risk of thyroid cancers induced in infancy emerges with an abrupt rise in incidence during adolescence, suggesting the possible influence of thyroid-stimulating hormone as a promoting factor.

If the epidemiology of radiation-induced thryoid and breast cancers are similar, there are major differences between aspects of breast cancer and of leukemia as reported in atomic bomb survivors[12] and patients irradiated for ankylosing spondylitis.[31] Specifically, (1) for the breast linearity appears to be a reasonable representation of dose response, while leukemia appears to be curvilinear.[8] (2) The Relative Biological Effectiveness (RBE) for neutron exposure and breast cancer is consistent with 1.0,[17] while for leukemia and all other radiogenic cancers it has much larger values.[8] (3) The human breast appears to be the only site for which fractionation or splitting of dose does not diminish risk,[3] while for leukemia fractionation reduces risk in practically all experimental situations.[24] (4) In contrast to the wave-like temporal pattern shown for radiation-induced leukemia,[12,31] there is no evidence that breast cancer risk decreases with time after reaching some maximum value.[3] (5) Finally, the relationship between age at exposure and risk differs dramatically for breast cancer compared with leukemia: on an absolute scale, radiogenic breast cancer risk appears to decrease with increasing age at exposure from menarche to menopause, whereas the risk for leukemia increases.[2,31] Pre-puberty exposures also appear to carry little or no radiogenic breast cancer risk, whereas for leukemia the greatest relative risk occurs at this time.[12] Elucidation of the reasons behind these differences may provide insights into the environmental and host determinants of cancer as well as suggest fresh ideas for future research.

Epidemiologic studies of radiation-induced cancer have led directly to cancer prevention through the setting of radiation protection guidelines for occupational, medical and public exposures. However, in the long run, perhaps the most important contributions will be the insights into basic

mechanisms of human carcinogenesis gained through such studies. The intensive epidemiologic evaluations of radiogenic cancer, while thus far few, have been productive of leads to such insights, and should be a major area of emphasis in cancer research in the immediate future.

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